

EXHIBIT 29

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**UNITED STATES DISTRICT COURT
CENTRAL DISTRICT OF CALIFORNIA
WESTERN DIVISION**

CENTOCOR, INC.,

Plaintiff,

v.

GENENTECH, INC. AND CITY OF
HOPE NATIONAL MEDICAL CENTER,

Defendants.

) Case No. CV 08-03573 MRP (CTx)

)

) The Honorable Mariana R. Pfaelzer

)

) **GENENTECH, INC.'S AND CITY
OF HOPE'S CORRECTED
OPENING BRIEF ON CLAIM
CONSTRUCTION**

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) Proposed Date: May 12, 2009

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) Time: TBD

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) Place: Courtroom 12

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CONSTRUCTION

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1 **I. INTRODUCTION**

2 Genentech and City of Hope set forth their proposed claim constructions for the
3 disputed terms in claims 18, 20, and 33 of U.S. Patent 6,331,415 to Cabilly *et al.* (“the
4 ‘415 patent”) and in claim 1 of U.S. Patent 6,417,335 to Basey *et al.* (“the ‘335
5 patent”).¹ Genentech and City of Hope have proposed a single phrase for construction
6 from the ‘415 patent: “transformed host cell comprising at least two vectors.” By
7 contrast, Centocor asks the Court to construe eight additional terms, almost all of
8 which were previously at issue in the *MedImmune* case.² Among them, Centocor
9 proposes separate (and redundant) constructions of “vector” and “transformed host
10 cell,” both of which are already contained in the entire phrase “transformed host cell
11 comprising at least two vectors.” And Centocor asks the Court to construe the word
12 “about” in the ‘335 patent, even though that word has an ordinary meaning and would
13 be readily understood by a jury.

14 Where required, Genentech and City of Hope offer constructions that track the
15 intrinsic evidence of the patent and the file history, read in light of the underlying
16 science. Centocor, in contrast, asks the Court to ignore the specification, to read
17 limitations into the asserted claims and, when all else fails, simply to rewrite them.
18 For example, Centocor proposes that the term “produced as separate molecules in a
19 single host cell” means “produced as separate molecules **while** in the single host cell”
20 (in an effort to create a non-infringement argument that claim 33 does not cover
21

22 ¹ Genentech and City of Hope assert claims 18, 20 and 33 of the ‘415 patent in this
23 action. Genentech is the sole assignee of the ‘335 patent and asserts claims 1, 2, 3
24 and 7 in this case.

25 ² One of the eight additional terms identified for construction by Centocor is
26 “variable domain.” Genentech and City of Hope do not believe this term requires
27 construction beyond its plain and ordinary meaning. If, however, the Court
28 believes it does, Genentech and City of Hope are willing to accept Centocor’s
proposal that, in the context of the ‘415 patent, “variable domain” means “the N-
terminal end of the heavy and light chains up to the beginning of the constant
domain.”

1 processes whereby the heavy and light chains are assembled to form an
2 immunoglobulin within a cell). That's not claim construction, it's claim revision.

3 Centocor's motivation for trying to narrow the scope of the claims isn't hard to
4 figure out. Properly construed, the claims are infringed – a fact that Centocor
5 effectively conceded by paying royalties under licenses to the '415 patent for over
6 seven years. The Court should construe the claims consistent with how Centocor
7 itself understood their scope prior to initiating this litigation.

8 **II. TECHNOLOGY BACKGROUND**

9 The two patents at issue in this case allow for the production of recombinantly-
10 engineered antibodies that can be administered therapeutically to patients. In the early
11 1980s, the inventors of the '415 patent had the insight that the nascent science of
12 recombinant DNA technology could be applied not just to express simple human
13 proteins of known therapeutic value, like human insulin, but also new types of
14 antibodies not found in nature to treat life-threatening diseases such as cancer. The
15 inventors of the '415 patent were the first to produce a recombinantly-engineered
16 antibody. They did so by transforming a single host cell with the genes coding for
17 both the heavy chain and the light chain of an immunoglobulin molecule and
18 expressing both chains in that cell. This method is now widely licensed and forms the
19 backbone of recombinant antibody production in the biotech industry. Genentech uses
20 this method to manufacture at least five of its commercial antibody products. Indeed,
21 for many years, Centocor paid royalties under the '415 patent for the antibody
22 products ReoPro and Remicade.

23 The '335 patent inventors likewise appreciated the promise of recombinantly-
24 engineered antibodies as therapeutics. Because recombinant antibodies are produced
25 in host cells that may contain viruses or other undesirable foreign proteins, it is
26 particularly important that the methods used to purify the antibodies be both very
27 precise as well as capable of working in a large-scale commercial setting. The '335

1 patent teaches and claims a method that overcomes these problems and can be used to
2 ensure that undesirable foreign proteins are not present in the ultimate product to be
3 administered to patients.

4 **A. The '415 Patent**

5 The asserted claims of the '415 patent recite a novel method of making
6 immunoglobulin molecules and immunologically functional immunoglobulin
7 fragments, as well as host cells transformed to make those molecules. As shown in
8 Figure 1 of the '415 patent, immunoglobulin molecules are proteins made up of four
9 chains (thus they are said to be "tetramers") and are typically represented
10 schematically as being Y-shaped. Declaration of Marcus E. Sernel ("Sernel Decl."),
11 Ex. A, '415 patent, Fig. 1, 3:17-38.³ The four protein chains include two "heavy"
12 chains and two "light" chains linked together by disulfide bonds. *Id.* at 3:33-38.

13 In nature, immunoglobulin molecules are produced by white blood cells. These
14 molecules can bind to a foreign substance such as a virus (called an antigen), thus
15 enabling the immune system to destroy it.

16 In the late 1970s and early 1980s, advances in genetic engineering allowed
17 scientists to begin making proteins in cells that do not normally express those
18 proteins. While some simple proteins had been recombinantly produced as of 1983,
19 the '415 inventors were the first to make antibodies using this new genetic
20 engineering technology. The '415 patent opened a new frontier in the treatment of
21 diseases, permitting the construction of novel antibodies not found in nature. These
22 recombinant antibodies can be designed to target particular antigens linked with
23 serious diseases such as cancer and autoimmune disorders.

24 The invention of the '415 patent is directed to methods, host cells, and vectors
25 for recombinantly producing immunoglobulin molecules or fragments. *Id.* at 5:30-38.

26 ³ Patent references are in the form "c:ll-ll," where "c" is the column number in the
27 specification and "ll-ll" is a range of line numbers.

1 A wide variety of cell types can be used as host cells for this recombinant production,
2 including bacterial and mammalian cell lines. *Id.* at 9:56-62, 10:26-29. The host cell
3 is transformed to include one or more vectors containing the immunoglobulin-
4 encoding DNA. *Id.* at 12:23-30. The vectors include DNA encoding for the heavy
5 and/or light chains of an immunoglobulin molecule, and (usually) additional DNA to
6 facilitate the expression of those genes.⁴ The '415 patent inventors recognized and
7 explained that the DNA encoding the heavy and light immunoglobulin chains could
8 be incorporated into a single vector or into two vectors. Sernel Decl., Ex. A at 12:26-
9 30.

10 The '415 patent describes several transformation methods suitable for
11 introducing one or more vectors into a range of different host cells. *See id.* at 10:33-
12 42. Host cells can be transformed by vectors that become integrated into their
13 chromosomal DNA or by vectors that remain as separate molecules. *Id.* at 8:7-9,
14 10:24-25. Whether a vector integrates into host cell chromosomal DNA depends on a
15 number of factors, including the type of host cell, the type of vector and, in some
16 cases, the conditions under which the host cell is maintained. In the case of bacterial
17 host cells, vectors will usually remain separate from the host cell DNA. Declaration
18 of Dr. Mary-Jane Gething ("Gething Decl.") ¶ 13. But there are exceptions. For
19 example, vectors based on a lambda phage can integrate into bacterial chromosomal
20 DNA. *See, e.g.,* Sernel Decl., Ex. B, Maniatis *et al.*, Molecular Cloning, A Laboratory
21 Manual, 17-26 (Cold Spring Harbor Laboratory Publications, 1982); Ex. C, M.
22 Gottesman & R. Weisberg, The Bacteriophage Lambda: Chapter 6—Prophage
23 Insertion and Excision, 113-138 (A.D. Hershey ed., Cold Spring Harbor Laboratory
24 Publications, 1971) (both discussing integrated lambda phage vectors); Gething Decl.

25
26 ⁴ This additional DNA in a vector can include an origin of replication, a promoter,
27 any necessary ribosome binding sites, RNA splice sites, polyadenylation sites, and
transcriptional terminator sequences. Sernel Decl., Ex. A at 9:66-10:3.

¶¶ 13-14. Even so, the integration of these lambda phage vectors can be reversed: increasing the temperature of the bacterial culture can cause the integrated vector to “pop out” and become an autonomous replicating element within the host cell. *See, e.g., Sernel Decl., Ex. B at 17; Gething Decl. ¶¶ 14-15.*

On the other hand, transformed mammalian host cells typically, although not always, include vectors that are integrated into the chromosomal DNA. Gething Decl. ¶¶ 17, 19. For example, the ’415 patent describes the SV40, pBR322 and polyoma vectors for use in transforming mammalian host cells, each of which will integrate into the host cell DNA. Sernel Decl., Ex. A at 8:62-9:15, 10:6-7, 28:56-57 (discussing the use of vectors derived from pBR322, including those with promoters derived from SV40 and polyoma); Ex. D, Rice and Baltimore, *Regulated Expression of an Immunoglobulin κ Gene Introduced into a Mouse Lymphoid Cell Line*, Proc. Natl. Acad. Sci. USA 79:7862-65, 7865 (1982) (noting the “SV40/pBR322 vector [] integrated into a presumably random site in the cell genome”); Ex. E, U.S. Patent No. 4,399,216 (the “Axel patent”), 24:8-56 (discussing the “rescue” of a pBR322 plasmid vector integrated into a mouse cell’s chromosomal DNA); Ex. F, Neer *et al.*, *Integration of Polyoma Virus DNA into Chromosomal DNA in Transformed Rat Cells Causes Deletion of Flanking Cell Sequences*, J. Gen Virol. 64, 69-82 (1983) (reviewing integrated polyoma vectors); Gething Decl. ¶¶ 17-18. Integrated vectors are usually required for a mammalian cell line to be stably transformed through many generations of cell culture. Gething Decl. ¶ 19. Indeed, virtually all commercial processes involving mammalian host cells for manufacturing therapeutic monoclonal antibodies employ the use of integrated vectors. *See Sernel Decl., Ex. S, Casnocha et al., Process Chemistry in the Pharmaceutical Industry, Volume 2: Chapter 26—Process Development Considerations for Therapeutic Monoclonal Antibodies in Mammalian Cell Culture*, 427-431, 435-436 (K. Gadamasetti *et al.* ed., CRC Press, 2008).

Moreover, even when integrated into the DNA of a mammalian cell, vectors can be “rescued” from – essentially, cut back out of – the mammalian host cell DNA. *See, e.g.*, Sernel Decl., Ex. E at 24:8-56 (discussing the “rescue” of a plasmid vector from a mouse cell transformed with said vector); Gething Decl. ¶¶ 20, 22. The recovered vector retains its ability to function within, and thus potentially transform, other host cells. *Id.* at 24:52-56 (explaining that the “rescued” plasmid vector retains its functionality post-rescue).

Because successful transformation of a host cell is a low-probability event – most host cells do not integrate and/or replicate the DNA introduced by a vector – host cells are ordinarily screened to identify the few cells that actually express the foreign DNA introduced by the vector. *See, e.g.*, Sernel Decl., Ex. A at 23:1-15 (describing how successfully transformed cells were identified based upon their resistance to ampicillin and tetracycline). By stimulating replication of these identified cells, a cell culture can be “grown” that consists entirely of transformed host cells expressing the immunoglobulin heavy and light chains for the immunoglobulin molecule of interest. *See id.* at 4:21-24, 12:31-39.

B. The '335 Patent

The '335 patent teaches an important step for purifying commercial quantities of antibodies using cation exchange chromatography. Whereas the '415 patent unleashed the potential of recombinantly producing a wide variety of antibodies on a grand scale, the '335 patent has helped make the economical production of safe, therapeutic products based on these antibodies a reality. The cation exchange chromatography methods claimed in the '335 patent are generally applicable to the purification of antibodies.

Like all proteins, antibodies are comprised of amino acids, which can have either a positive or negative charge depending on the pH of the surrounding solution. At a given pH, an antibody will have a distribution of positively and/or negatively

1 charged amino acid residues on its surface. Different proteins will likely have
2 different charge characteristics at that same pH. Cation exchange chromatography
3 takes advantage of the fact that, at a given pH, the antibody to be purified has different
4 charge characteristics from the contaminants.

5 In cation exchange chromatography, a column is filled with "cation exchange
6 resin," which often comprises very small negatively-charged beads or particles.
7 Cation exchange chromatography exploits the principle that opposite charges attract
8 one another. If a solution containing a positively-charged product and an uncharged
9 or negatively-charged contaminant is passed through a cation exchange column, the
10 positively-charged product will bind to the resin and the contaminant will pass
11 through the column. This separates the product from the contaminant and purifies the
12 product.

13 The '335 patent relates to particular methods for using cation exchange
14 chromatography to purify antibodies. First, a composition containing the antibody to
15 be purified and one or more contaminants is allowed to flow through a column
16 containing cation exchange resin. The claims of the '335 patent specify an optimal
17 range for the milligrams of antibody to be loaded onto the column for each milliliter
18 of cation exchange resin. As the composition flows through the column, the
19 positively-charged antibody will bind to the negatively-charged cation exchange resin,
20 while uncharged and negatively-charged contaminants flow through the column.
21 Second, in order to remove any positively-charged contaminants that, in addition to
22 the desired antibody, also bind to the negatively-charged resin, an intermediate wash
23 solution may be used to elute the contaminants from the column without eluting
24 significant amounts of the desired antibody. This can be accomplished, for example,
25 by changing the pH of the intermediate wash solution so that the antibody remains
26 positively charged while a contaminant becomes neutral or negatively charged. Third,
27 the antibody is eluted from the column by flowing a solution through the column that

1 removes the antibody from the cation exchange resin. This cation exchange
2 chromatography process as claimed in the '335 patent has proven to be a critical step
3 in producing therapeutic antibody products in an economical and safe manner.

4 **III. LEGAL STANDARD GOVERNING CLAIM CONSTRUCTION**

5 The claims of a patent “define the invention to which the patentee is entitled the
6 right to exclude.” *Phillips v. AWH Corp.* 415 F.3d 1303, 1312 (Fed. Cir. 2005) (*en*
7 *banc*) (quoting *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d
8 1111, 1115 (Fed. Cir. 2004)). Typically, the words of a claim are ““given their
9 ordinary and customary meaning,”” which is the “meaning that the term would have to
10 a person of ordinary skill in the art in question at the time of the invention....” *Id.* at
11 1312-13. (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed.
12 Cir. 1996)). This person, however, is deemed to read the term “not only in the context
13 of the particular claim in which the disputed term appears, but in the context of the
14 entire patent....” *Id.* at 1313. Indeed, “the context in which a term is used in the
15 asserted claim can be highly instructive.” *Id.* at 1314. Accordingly, “[o]ther claims of
16 the patent in question, both asserted and unasserted, can also be valuable sources of
17 enlightenment as to the meaning of a claim term.” *Id.*

18 Because the claims are part of a “fully integrated written instrument” that
19 includes the specification, the claims “must be read in view of the specification, of
20 which they are part.” *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 978-79
21 (Fed. Cir. 1995). At the same time, however, limitations from the specification may
22 not be read into the claims. *Phillips*, 415 F.3d at 1323. Recognizing the tension
23 between these two important principles, the Federal Circuit has explained that
24 “[a]bsent a clear disclaimer of particular subject matter, the fact that the inventor may
25 have anticipated that the invention would be used in a particular way does not mean
26 that the scope of the invention is limited to that context.” *Liebel-Flarsheim Co. v.*
27 *Medrad, Inc.*, 358 F.3d 898, 909 (Fed. Cir. 2004) (quoting *Northrop Grumman Corp.*

1 v. *Intel Corp.*, 325 F.3d 1346, 1355 (Fed. Cir. 2003)). Indeed, “even when the
2 specification describes only a single embodiment, the claims of the patent will not be
3 read restrictively unless the patentee has demonstrated a clear intention to limit the
4 claim scope using ‘words or expressions of manifest exclusion or restriction.’” *Id.* at
5 906 (quoting *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1327 (Fed. Cir.
6 2002)).

7 In addition to the specification, a court must also consider the prosecution
8 history of a patent as part of its claim construction analysis. *Markman*, 52 F.3d at
9 980. The prosecution history “is often of critical significance in determining the
10 meaning of the claims” because it “contains the complete record of all the proceedings
11 before the Patent and Trademark Office, including any express representations made
12 by the applicant regarding the scope of the claims.” *Vitronics*, 90 F.3d at 1582. Like
13 the specification, the prosecution history provides evidence of how the Patent Office
14 and the inventor understood the patent. See *Lemelson v. Gen. Mills, Inc.*, 968 F.2d
15 1202, 1206 (Fed. Cir. 1992).

16 Finally, the Court may refer to extrinsic evidence, including expert testimony,
17 to “help educate the court regarding the field of the invention” and to help “determine
18 what a person of ordinary skill in the art would understand the claim terms to
19 mean....” *Phillips*, 415 F.3d at 1319. Extrinsic evidence is useful to confirm that the
20 interpretation the intrinsic evidence mandates “is not inconsistent with clearly
21 expressed, plainly apposite, and widely held understandings in the pertinent technical
22 field.” *Pitney Bowes v. Hewlett-Packard Co.*, 182 F.3d 1298, 1309 (Fed. Cir. 1999).

IV. CONSTRUCTION OF THE DISPUTED CLAIM TERMS

A. The '415 Patent

1. "transformed host cell comprising at least two vectors"

Genentech and City of Hope's Proposed Construction	Centocor's Proposed Construction
host cell whose heritable DNA has been altered to include foreign DNA from at least two DNA constructs	a cell into which foreign DNA has been introduced comprising at least two separate DNA molecules that are capable of transporting a DNA segment into another cell

Genentech and City of Hope's proposed construction gives the claims their proper scope and is compelled by the language of the claims, the specification, and the underlying science. Claim 18 is directed to a host cell that has been transformed to include two vectors. It is a matter of scientific fact, expressly contemplated in the '415 patent specification, that vectors can be present as episomal (*i.e.*, separate) elements or as part of the chromosomal DNA both in transformed bacterial and mammalian host cells. These vectors all fall within the scope of the invention and the claims – and the claims must be interpreted in a manner consistent with that well-understood scientific fact.

Centocor, however, wants to limit the claims to an embodiment in which the vectors do not integrate into the host cell's DNA. Centocor's motivation for taking this position is obvious: Centocor wants to argue that it doesn't infringe claims 18 and 20 because it does so using a stable cell line in which the vector DNA is integrated into the chromosomal DNA. *See* Sernel Decl., Ex S at 429, 435. Thus, applying its proposed claim construction, Centocor would argue that it cannot infringe claims 18 and 20 because the vectors no longer exist as "separate molecules." Centocor's effort to limit the scope of these claims to host cells in which the vectors

1 continue to exist as “separate molecules” conflicts with the specification and leads to
2 illogical results.

3 (a) **The intrinsic evidence supports Genentech’s proposed**
4 **construction.**

5 Claim 18 is directed to a host cell that is transformed to include two vectors. It
6 covers a range of host cells including both bacterial and mammalian host cells (as
7 claim 20 makes explicit). Claim 18 does not specify whether the vectors in the
8 transformed host cell are separate from or integrated into the host cell’s chromosomal
9 DNA. But regardless of whether they are integrated or not, the presence of the vectors
10 is necessary for the host cell to be transformed. Sernel Decl., Ex. A at 8:6-9
11 (disclosing that replicable vectors are operable regardless of whether they are
12 integrated); Gething Decl. ¶¶ 11, 19. If the vectors are not present, the host cell is not
13 transformed.

14 The specification of the ’415 patent confirms that Defendants’ proposed
15 construction is correct. The patent explicitly discloses that the vectors of the invention
16 can be integrated into the host cell chromosomal DNA: “*if the vector is integrated*
17 *into the host cell chromosome, the [host cell’s origin of replication] is often sufficient*
18 *[for replication].*” Sernel Decl., Ex. A at 10:24-25 (emphasis added). The patent
19 similarly states that the “expression vectors” of the invention “*must be replicable in*
20 *host organisms either as episomes or as an integral part of the chromosomal DNA.*”
21 *Id.* at 8:7-9 (emphasis added). Genentech and City of Hope’s construction tracks
22 these requirements from the specification. Because expression vectors are one type of
23 vector,⁵ at least one class of “vectors” included within claim 18 must be able to

24
25 ⁵ All expression vectors are vectors even if not all vectors are expression vectors.
26 So if an expression vector can be an integral part of the chromosomal DNA, then at
27 least some (though not necessarily all) vectors covered by claim 18 can be an
28 integral part of the chromosomal DNA. Centocor’s construction is inconsistent
with the specification’s definition of an expression vector.

1 integrate into the host cell's chromosomal DNA.⁶ Genentech and City of Hope's
2 construction thus accords with the intrinsic evidence.

3 (b) **Centocor's proposed construction contradicts the**
4 **intrinsic evidence and ignores scientific reality.**

5 Centocor's effort to read additional limitations into the claim is inconsistent
6 both with the specification and with governing claim construction principles. *First*,
7 Centocor would require that the vectors of claim 18 continue to exist as separate
8 molecules even after they have transformed the host cell. *Second*, Centocor would
9 require that, even after the vectors have introduced foreign DNA into the host cell,
10 they retain the ability to transport a DNA segment into *another* host cell. *Third*,
11 Centocor would apparently equate a "transformed host cell" with any cell into which
12 foreign DNA has been introduced, whether or not that DNA is passed on to daughter
13 cells as part of the host cell's DNA.

14 *First*, Centocor improperly seeks to limit the scope of claim 18 (and of claim
15 20, which depends from it) to transformed host cells in which the vectors are not
16 integrated into the host cell DNA. Nothing in the specification suggests an intent to
17 limit the scope of the claims in this way; to the contrary, it explicitly contemplates that
18 vectors can be integrated, and teaches the use of vectors that are known to integrate.
19 Sernel Decl., Ex. A at 10:24-25 (referring to a vector "integrated into the host cell
20 chromosome"). For example, the '415 patent specifically discusses the use of vectors
21 that were known at the time to integrate into mammalian chromosomal DNA. *Id.* at

22 ⁶ That definition from the specification is also consistent with the usage in the art.
23 For example, in 1985 the Department of Human Health and Services ("HHS")
24 issued a draft of Points to Consider relating to the production and testing of new
25 drugs produced by recombinant DNA technology. One of the requirements was
26 that "*the physical state of the vector inside of the host cell, integrated or*
27 *extrachromosomal, should be provided.*" Sernel Decl., Ex. G, Department of
28 Human Health and Services Draft Points to Consider in the Production and Testing
of New Drugs and Biologicals Produced by Recombinant DNA Technology, 5
(1985) (emphasis added). Thus HHS, like the '415 patent inventors, recognized
that vectors may exist in the host cell in either integrated or extrachromosomal
form.

1 8:62-9:15, 10:6-7, 28:56-57 (discussing the use of vectors derived from pBR322,
2 including those with promoters derived from SV40 and polyoma); Ex. D at 7865
3 (noting the “SV40/pBR322 vector [] integrated into a presumably random site in the
4 cell genome”); Ex. E at 24:8-56 (noting that the bacterial plasmid, pBR322, “stably
5 integrated into the mouse genome via transformation”); Ex. F at 69 (discussing
6 polyoma vectors integrated into the chromosomal DNA); Gething Decl. ¶¶ 17-18.
7 These integrated vectors would be particularly preferable to create “permanent
8 [mammalian] cell lines” to be “scale[d]-up for large preparations.” Sernel Decl., Ex.
9 A. at 4:44-50; Gething Decl. ¶ 19. Centocor’s proposed construction would exclude
10 these specifically disclosed embodiments and should, therefore, be rejected. *See*
11 *Oatey v. IPS Corp.*, 514 F.3d 1271, 1276-77 (Fed. Cir. 2008) (holding that a claim
12 construction that excludes embodiments disclosed in the specification is correct only
13 if there is a clear disclaimer of the excluded embodiments by the patentee); *Osram*
14 *GMBH v. ITC*, 505 F.3d 1351, 1358 (Fed. Cir. 2007) (rejecting claim construction in
15 part because it would exclude the patentee’s products that the patent was intended to
16 cover); *MBO Labs., Inc. v. Becton, Dickinson & Co.*, 474 F.3d 1323, 1333 (Fed. Cir.
17 2007) (reversing district court’s claim construction because it excluded embodiments
18 disclosed in the specification); *Lava Trading, Inc. v. Sonic Trading Mgmt.*, 445 F.3d
19 1348, 1353-55 (Fed. Cir. 2006) (reversing district court’s claim construction because
20 it excluded embodiments disclosed in the specification).

21 Centocor’s proposed construction also makes no sense in light of the fact that
22 the “separateness” of a vector in a host cell can change over time and be influenced by
23 factors such as the temperature at which the host cell is maintained. Even after
24 integration, vectors can emerge from the chromosomal DNA and become separate
25 molecules. *See, e.g.*, Sernel Decl., Ex. B at 22 (describing the de-integration of the
26 bacteriophage λ vector); Gething Decl. ¶¶ 14-15, 20-21. This de-integration can be
27 caused by events such as changes in temperature. *Id.* In Centocor’s view, host cells

1 with integrated vectors would fall outside the scope of claim 18, but might become
2 infringing if those vectors emerged from the chromosomal DNA to become separate
3 molecules. It makes no sense that the Cabilly inventors would define, or anyone else
4 would understand, the scope of claims 18 and 20 in this way.

5 The Axel patent (U.S. Patent No. 4,399,216), which is part of the intrinsic
6 record (because it is a cited reference from the reexamination), also confirms that a
7 vector remains a vector even when it is integrated into the host cell chromosomal
8 DNA. Axel discusses the “rescue” of a “vector,” pBR322, after it was “stably
9 integrated into the mouse genome via transformation.” Sernel Decl., Ex. E at 24:11-
10 56; Gething Decl. ¶ 22. Thus, Axel uses the term “vector” to describe the vector
11 after it was integrated into the mouse DNA. And Axel also demonstrates that the
12 vector can be pulled out of the chromosomal DNA of the host cell, even after it has
13 been integrated. Sernel Decl., Ex. E at 24:51-56. On the other hand, according to
14 Centocor, the vector exists before it is used to transform the host cell, then ceases to
15 exist when it is integrated, then exists again as a “vector” after it is rescued (or
16 otherwise emerges from the chromosomal DNA). But vectors are not such ephemeral
17 things. To the contrary, the fact that a vector can be rescued from a host cell into
18 which it has been integrated shows that the vector was there all along, even though it
19 was not a “separate molecule.”

20 *Second*, Centocor wants to read in an explicit limitation that the vectors must be
21 “reusable” – that they retain the ability to transform a different host cell in the future.
22 Nothing in the claims or the specification suggests such a requirement. The claims
23 simply require that the host cell be transformed by the vectors. In other words, the
24 alteration of the cell’s heritable DNA by the presence of the vectors is what makes the
25 host cell a transformed host cell. See Sernel Decl., Ex. A at 8:28-32. If the vectors
26 are removed from the host cell, the host cell is no longer transformed. Gething Decl.
27 ¶¶ 11, 19. Thus the “transformational” quality of a vector, once it is in a host cell, lies

1 in its ability to keep the host cell in the state of being transformed, not whether it has
2 the ability to be reused to transform new and different cells in the future. *Id.*

3 **Third**, Centocor proposes that claim 18 encompass any “cell into which foreign
4 DNA has been introduced.” That construction is apparently intended to sweep in cells
5 that are not host cells in order to try to read the claims on long-standing hybridoma
6 technology. That is contrary to the specification’s clear teaching that it is offering an
7 improvement over existing hybridoma technology. Sernel Decl., Ex. A at 2:40-3:2
8 (noting the disadvantages of prior art hybridoma technology). It is also fundamentally
9 inconsistent with other patents from the early 1980s that reflect this understanding of
10 what it means to be transformed. *See, e.g.*, Sernel Decl., Ex. H, U.S. Patent No.
11 3,930,956, 1:21-24 (“Transformation is the heritable modification of the properties of
12 one strain of microorganism (acceptor) by deoxyribonucleic acid (DNA) extracted
13 from the cells of another strain of microorganism (donor).”); Ex. I, U.S. Patent No.
14 4,302,544, 1:55-60 (“In order to be useful for recombinant DNA technology, the
15 microorganism (host) must be capable of undergoing ‘transformation,’ i.e., itself be
16 capable of incorporating DNA and yielding a viable microorganism capable of
17 expressing the traits encoded by the newly inserted genes.”); Ex. J, U.S. Patent No.
18 4,363,877, 13:64-68 (“Transformation, as is understood in the art and used herein, is
19 the term used to denote the process whereby a microorganism incorporates
20 extracellular DNA into its own genetic constitution.”); Ex. K, U.S. Patent No.
21 4,727,028, 2:37-40 (“Transformation—the introduction of DNA into a recipient host
22 cell that changes the genotype and consequently results in a stable and heritable
23 change in the recipient cell.”). As a result, the Court should construe the claim term
24 as requested by Genentech and City of Hope to mean a “host cell whose heritable
25 DNA has been altered to include foreign DNA from at least two DNA constructs.”

26 **Other terms within the broader phrase**

27 Centocor also argues that individual words in this broader phrase – “vector” and

“transformed host cell” – need to be construed separate and apart from the phrase in which they appear. But Centocor has offered no good reason for the Court to undertake that task (aside from its transparent desire to construct non-infringement arguments). What matters, and all that matters, is the scope of the claim. The parties have proposed competing constructions that would resolve all disputes as to claim scope. There’s no reason for the Court to go further.

2. “immunoglobulin”

Genentech and City of Hope’s Proposed Construction	Centocor’s Proposed Construction
<i>No construction needed.</i>	a tetrameric molecule consisting of two longer polypeptide chains called heavy chains and two shorter polypeptide chains called light chains, or aggregates of such tetrameric molecules, whether or not specific immunoreactive activity is a property

The term “immunoglobulin” does not require any construction separate and apart from the term “immunoglobulin molecule,” discussed below. Aside from its use in the phrase “immunoglobulin molecule,” “immunoglobulin” only appears in claims 18 and 33 in the terms “immunoglobulin fragment,” “immunoglobulin heavy chain,” and “immunoglobulin light chain.” These terms simply refer to a fragment of an immunoglobulin molecule, to the heavy chain of the immunoglobulin molecule, and to the light chain of the immunoglobulin molecule, respectively. There is no dispute between the parties as to the meaning of “fragment,” “heavy chain,” or “light chain,” nor is there any dispute that an immunoglobulin molecule is composed of heavy and light chains. As such, the term “immunoglobulin,” standing alone, does not require construction.

3. "immunoglobulin molecule"

Genentech and City of Hope's Proposed Construction	Centocor's Proposed Construction
tetrameric molecule consisting of two longer polypeptide chains called heavy chains and two shorter polypeptide chains called light chains, or aggregates of such tetrameric molecules, capable of binding to a known antigen , whether or not specific immunoreactive activity is a property	a tetrameric molecule consisting of two longer polypeptide chains called heavy chains and two shorter polypeptide chains called light chains, or aggregates of such tetrameric molecules, whether or not specific immunoreactive activity is a property

Genentech does not believe that the term immunoglobulin molecule requires any construction. However, Genentech is willing to agree to Centocor's proposed construction, with one important modification to make the construction consistent with the intrinsic evidence. The parties agree that the term requires a tetrameric molecule consisting of two heavy chains and two light chains and does *not* require specific immunoreactivity to be a property. The sole substantive difference between the parties' proposed constructions is whether an immunoglobulin molecule must be "capable of binding to a known antigen." The prosecution history confirms that requirement. Indeed, the Patent Office, when recently issuing its Notice of Intent to Issue *Ex Parte* Reexamination Certificate ("NIRC") reaffirming the patentability of the '415 patent claims, explained that the claimed "immunoglobulin molecule" must be "capable of binding to a known antigen." Sernel Decl., Ex. L, Feb. 23, 2009 NIRC, 3. The Court should similarly include this language in its construction of this term.

During prosecution, including during prosecution of the parent application which issued as U.S. Patent No. 4,816,567, the patentees repeatedly distinguished their invention from the prior art on this point, among others. The patentees

1 specifically explained that:

2 while DNA encoding an immunoglobulin encoding any
3 immunoglobulin is readily available in myelomas (which
4 produce large amounts of immunoglobulin that binds to an
5 antigen only known to the cancer), it would not have been
6 reasonably predictable that DNA encoding a known antigen
7 specific immunoglobulin could be obtained. No art of record
8 discloses cloning an immunoglobulin having specificity for a
9 known antigen.

10 Sernel Decl., Ex. M, May 26, 1987 Office Action Resp., 13.

11 In a subsequent response to the Patent Office, the patentees once again
12 emphasized that the capability of binding a known antigen was one of the
13 distinguishing aspects of the immunoglobulin molecules of their invention:

14 [t]he art of record fails to disclose an immunoglobulin gene
15 which could be expressed to produce an immunoglobulin chain
16 capable of binding to a predetermined, known antigen. . . .
17 Even if the prior art immunoglobulins bound to some antigen,
18 the references themselves do not make it known. The
19 “inherent” capability of the myeloma immunoglobulins is that
20 they have regions that appear to be variable domains. Whether
21 they in fact bind any antigen is speculative. That they do not
22 bind to a known antigen is certain.

23 Sernel Decl., Ex. N, May 9, 1988 Office Action Resp., 4-5 (emphasis in original).

24 In *Genentech, Inc. v. Celltech Therapeutics, Ltd.*, Case No. C98-3926 MMC,
25 the § 146 action that followed Interference No. 102,572, both Genentech and Celltech
26 contended that the phrase “Ig molecule or immunologically functional Ig fragment”
27 should be construed to mean an immunoglobulin molecule or fragment that is capable

1 of binding to a known antigen. The dispute between the parties was only as to what
2 level of binding specificity the count required.⁷ See, e.g., Sernel Decl., Ex. O,
3 Genentech's Motion to Construe the Count, 11 (explaining that the count required
4 production of "an 'immunologically functional' Ig molecule or fragment, where
5 'immunologically functional' means capable of binding to a selected, predetermined
6 antigen"); Ex. P, Genentech's Reply Supporting its Motion to Construe the Count, 6, 8
7 (reiterating that an immunoglobulin molecule is "capable of binding with a selected,
8 predetermined antigen" and arguing that an immunoglobulin fragment can be
9 "completely functional' without specifying any particular affinity or specificity").

10 The express definition of "immunoglobulin molecule" provided by the PTO in
11 its recently-issued NIRC confirms that this term requires a capability of binding to a
12 known antigen. As the Court is aware, the '415 patent has been under reexamination
13 since 2005. On February 23, 2009, the Patent Office issued a NIRC confirming the
14 patentability of all claims of the '415 patent, subject to minor amendments (to claims
15 not asserted or otherwise relevant here). In the NIRC, the PTO stated:

16 Based on the prosecution history of the patent at issue, and the
17 interference record from Interference No. 102,572, the term
18 "immunoglobulin molecule" in claims 1 and 33 is considered
19 to be [an] immunologically functional molecule and capable of
20 binding to a known antigen.

21 Sernel Decl., Ex. L at 3.

22 Courts give significant weight to statements by the PTO in issuing NIRCs or
23 similar statements confirming patentability. See, e.g., *ACCO Brands, Inc. v. Micro*
24 *Sec. Devices, Inc.*, 346 F.3d 1075, 1078-79 (Fed. Cir. 2003) (adopting claim

25 ⁷ The count, which included the phrase "Ig molecule or immunologically
26 functional Ig fragment," was substantively identical to issued claims 1 and 33 of
27 the '415 patent. Compare Sernel Decl., Ex. O at 6 with Ex. A at 28:36-49, 30:30-
42.

construction set forth in the NIRC); *Gussin v. Nintendo of Am., Inc.*, 1995 WL 460566 at *5-6 (Fed. Cir. 1995) (construing term consistently with statements in the NIRC) (*unpublished disposition*); *Boston Scientific Corp. v. Cordis Corp.*, 2006 WL 2432599 at *4 (N.D. Cal. Aug. 21, 2006) (rejecting proposed construction inconsistent with the NIRC); *C.R. Bard, Inc. v. U.S. Surgical Corp.*, 102 F. Supp.2d 199, 217 (D. Del. 2000) (adopting construction based on examiner's conclusions in the NIRC).

Centocor has offered no reason to deviate from the PTO's definition and exclude the phrase "capable of binding to a known antigen" in defining the term "immunoglobulin molecule." Accordingly, to prevent the risk of jury confusion and ensure that the scope of the claims is properly defined, the term "immunoglobulin molecule" should be construed to explicitly include the limitation "capable of binding to a known antigen."

4. "immunologically functional immunoglobulin fragment"

Genentech and City of Hope's Proposed Construction	Centocor's Proposed Construction
portion of an immunoglobulin molecule that is capable of binding to a known antigen	a portion of an immunoglobulin molecule that is capable of binding to antigen

Genentech and City of Hope believe that the parties agree on the construction of this term, subject to the resolution of the proper construction of "immunoglobulin molecule" and whether it requires binding to a known antigen.

5. "produced as separate molecules in a single host cell"

Genentech and City of Hope's Proposed Construction	Centocor's Proposed Construction
<i>No construction needed.</i>	the heavy and light chains of the immunoglobulin molecule are produced as separate molecules while in the single host cell

1 Centocor has not offered any reason why this phrase requires construction. The
2 claim requires what it says – the heavy chain and the light chain are produced as
3 separate molecules in the host cell. The claim does not specify what happens to those
4 chains after they are produced. Indeed, Centocor’s proposed construction of this
5 phrase repeats all of the words of the claim, which raises the question why Centocor
6 thinks that the phrase requires construction in the first place. After all, this Court
7 concluded in *MedImmune* that it didn’t, and Genentech and the City of Hope agree.

8 Rather than construing the words that appear in the claim, Centocor has simply
9 rewritten the claim to add the word “while.” So, instead of requiring that the chains
10 be “produced as separate molecules in the single host cell,” Centocor proposes that the
11 claim be redrafted to require that the chains be “produced as separate molecules *while*
12 in the single host cell.” A construction that does not actually construe the claim, but
13 instead redrafts it, is unlikely to be either necessary or correct.

14 Centocor’s motivation for adding the word “while” to the claim is not hard to
15 figure out – Centocor wants to make it appear that the claim requires that the chains
16 remain separate so long as they are in the host cell. Centocor’s need to add a word to
17 the claim in order to introduce this concept should be sufficient to make clear that the
18 concept is not in the claim itself. *Helmsderfer v. Bobrick Washroom Equip., Inc.*, 527
19 F.3d 1379, 1383 (Fed. Cir. 2008) (“Courts cannot rewrite claim language.”). The
20 Court reached just that conclusion in *MedImmune*, rejecting a proposed construction
21 that was similar in substance, though worded differently, precisely because that
22 construction (or, more accurately, addition) could not be reconciled with the language
23 of the claim.

24 Centocor’s implication that the chains must remain separate “while” they are in
25 the host cell is inconsistent not only with claim 1 (and claim 33), but also the claims
26 that depend from claim 1. Claim 9 discloses a process according to claim 1 “wherein
27 the immunoglobulin heavy and light chains are expressed as separate molecules in the

1 host cell and secreted therefrom as an immunologically functional immunoglobulin
2 molecule or immunoglobulin fragment.” So, in claim 9, the heavy and light chains
3 exit the host cell as an assembled molecule, and thus must have been assembled inside
4 the cell. Claim 9 thus contemplates that the chains are produced as separate molecules
5 *in* the host cell, but not that they remain as separate molecules *while* in the host cell.

6 Centocor’s effort to rewrite claim 9 is not only inconsistent with what claim 9
7 actually says, it also runs smack into claim 10, which discloses a process “wherein the
8 immunoglobulin heavy and light chains are produced in insoluble form and are
9 solubilized and allowed to refold in solution to form an immunologically functional
10 immunoglobulin molecule or immunoglobulin fragment.” In other words, claim 10
11 contemplates that the chains exit the host cell as separate molecules. In order to give
12 both claim 9 and claim 10 distinct scopes, they must be read as providing for two
13 alternates – that the chains combine either inside or outside the host cell – both of
14 which are embraced within claim 1. *Curtiss-Wright Flow Control Corp. v. Velan,*
15 *Inc.*, 438 F.3d 1374, 1380 (Fed. Cir. 2006) (noting that the doctrine of claim
16 differentiation generally is a “presumption that each claim in a patent has a different
17 scope”) (citing *Versa Corp. v. Ag-Bag Int’l Ltd.*, 392 F.3d 1325, 1330 (Fed. Cir. 2004)
18 (quoting *Comark Commc’ns, Inc. v. Harris Corp.*, 156 F.3d 1182, 1187 (Fed. Cir.
19 1998))).

20 **Other term within the broader phrase**

21 Centocor also seeks a separate construction for the term “in a single host cell.”
22 But just as the broader phrase “produced as separate molecules in a single host cell”
23 requires no construction, the embedded phrase “in a single host cell” similarly does
24 not. This is a straightforward term that should be given its ordinary and plain
25 meaning. Instead, Centocor seeks to distort the term’s meaning by proposing that “in
26 a single host cell” be defined to mean “a single cell into which foreign DNA has been
27 introduced.” Oddly, Centocor’s proposed construction for “in a single host cell” is

identical to its proposal for “transformed host cell” (except for the term “single”), and leads to the nonsensical result that *all* host cells must be *transformed* host cells. This cannot be correct. The Court should reject Centocor’s invitation to import meaning into this straightforward phrase. The plain meaning of “in a single host cell” will suffice and should be adopted.

B. The ‘335 Patent

1. “about”

Genentech’s Proposed Construction	Centocor’s Proposed Construction
<i>No construction needed.</i>	within the range of experimental error that occurs in any measurement

The word “about” appears in claim 1 of the ‘335 patent in the phrase “from about 20 mg to about 35 mg....” Sernel Decl., Ex. Q, ‘335 patent, 29:7-8. It is a simple, non-technical word that is readily understood and requires no further definition or construction. Genentech thus proposes that it be understood according to its plain and ordinary meaning, which has been widely endorsed by the courts. *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1372 (Fed. Cir. 2005) (holding that “the term ‘about’ should be given its ordinary and accepted meaning of ‘approximately’”); *see also Ortho-McNeil Pharm., Inc. v. Caraco Pharm. Labs., Ltd.*, 476 F.3d 1321, 1326 (Fed. Cir. 2007) (noting that the parties and the district court agreed that “about” means “approximately”); *Conopco, Inc. v. May Dept. Stores Co.*, 46 F.3d 1556, 1561 (Fed. Cir. 1994) (refusing to construe “about” to extend beyond its ordinary meaning); *ACCO Brands USA LLC v. Secucomputer, Inc.*, 2008 WL 2566863 at *3 (N.D. Ill. June 25, 2008) (declining to construe “about” beyond its ordinary meaning). Although a patentee can sometimes act as her own lexicographer and define a term to mean something other than its common meaning, nothing in the

1 intrinsic evidence suggests that the '335 patentees redefined the term "about." *See*
2 *Merck*, at 1370, 1372 (noting that the patentee may act as his own lexicographer and
3 define a term to mean something other than its ordinary meaning, but concluding that
4 the patentee did not do so with respect to "about"). As a result, the Court need not
5 construe it.

6 Centocor's proposed construction would replace this common and readily
7 understood word with an eleven-word phrase that is ambiguous and nowhere
8 suggested by the intrinsic evidence. Centocor seeks to read into the claim concepts
9 relating to "experimental error" and "any measurement," making the term "about"
10 depend on a number of factors not specified in the claims or addressed in the
11 specification. There is no intrinsic evidence suggesting that the term "about" depends
12 on any particular measurement device, measurement protocol, or experimental error.
13 And there is no reason to inject this ambiguity into the claims. The commonly
14 understood meaning of "about" should apply in this case.

15 **V. CONCLUSION**

16 For the foregoing reasons, Genentech and City of Hope respectfully submit that
17 the disputed terms should be construed according to their proposals, which clearly and
18 accurately define the scope of the asserted claims according to the intrinsic evidence.
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1 **PROOF OF SERVICE**

2
3 I, Mindy A. Marshall, am employed in the County of Cook, State of Illinois. I
4 am over the age of 18 and not a party to the within action. My business address is 200
5 E. Randolph Street, Chicago, Illinois 60601.

6 On April 2, 2009, I served a true copy of the following documents described as:

7 **GENENTECH, INC'S AND CITY OF HOPE'S**
8 **CORRECTED OPENING BRIEF ON CLAIM**
9 **CONSTRUCTION**

on the interested parties in this action as follows:

10
11 ☒ **By E-Mail:** I caused to have delivered such documents to the addressees as set
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